

Combined Radiation and Chemotherapy for Advanced Undifferentiated Nasopharyngeal Carcinoma in Children

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Five children, 11–16 years of age at diagnosis, with advanced (stage IV) undifferentiated nasopharyngeal carcinoma, are reviewed. All had radiotherapy and chemotherapy, four at first treatment, are disease free in 8 months, 6, 10, and 13 years from diagnosis. One patient who had radiotherapy only as primary treatment and chemotherapy for metastases, died 15 months from diagnosis. One patient who received 60 Gy and chemotherapy according to the BACON protocol had severe early toxic-

ity and severe late sequelae of treatment. Three patients who received chemotherapy according to a modified UICC-2 protocol for nasopharyngeal carcinoma and 50 to 54 Gy to the primary site had only mild early toxicity and mild late effects of treatment. With lower radiation doses, adjusted to the effect of preradiation chemotherapy, complete tumor control was achieved and acute and long-term morbidity reduced. *Med. Pediatr. Oncol.* 28:366–369, 1997. © 1997 Wiley-Liss, Inc.

Key words: nasopharyngeal carcinoma; childhood cancer; chemotherapy; radiotherapy

INTRODUCTION

Nasopharyngeal carcinoma is rare, although one of the most frequent epithelial tumor in children [1]. Commonly, it is of the undifferentiated type, a histological pattern associated with advanced loco-regional disease at presentation [2] and with a higher rate of distant metastases [3–5].

High-dose radiation therapy is sufficient only for local and regional control of disease [1,4–7]. Because of the biological characteristics of the tumor, systemic therapy is necessary. Several reports have proved chemotherapy to be effective when added to radiation as initial treatment; however, the role of adjuvant chemotherapy in this disease remains unclear [8–14]. Some of the authors also suggested, that such combined therapy allows a reduction of radiation dose to minimize the risk for late sequelae, with retained loco-regional tumor control [8,9]. However, the series of children with undifferentiated nasopharyngeal carcinoma (UNC) are very small and experience limited.

We wish to report our experience with five patients who had histologically verified advanced undifferentiated nasopharyngeal carcinoma and were treated with a combination of radiotherapy and chemotherapy.

PATIENTS AND METHODS

Between 1972 and 1995, 5 children with histologically proven undifferentiated nasopharyngeal carcinoma

were diagnosed and treated with radiotherapy and chemotherapy at the Institute of Oncology and/or University Hospital of Pediatrics, Hematology Oncology Department, in Ljubljana, Slovenia.

The diagnostic work-up included clinical examination, plain film radiography, and tomography of the nasopharynx, direct nasopharyngoscopy, chest radiography, bone and liver scan. The anatomical extent of disease at diagnosis was evaluated retrospectively according to the UICC TNM classification [15].

Of four boys, two were 15, two 11, and 16 and the girl was 13 years old. Cervical lymphadenopathy was the first symptom in all. Three patients had nasal obstruction or epistaxis and two had headache; three had earache or hearing impairment. The interval between the onset of symptoms and diagnosis was 1–11 months. All tumors were regionally and/or locally advanced (stage IV). No patient had distant metastases at the time of treatment (Table 1).

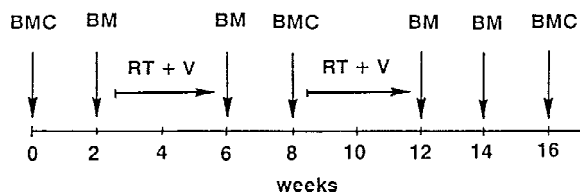
The surgical procedure was limited to biopsy in four patients. In patient no. 4, a right-sided functional radical

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B - bleomycin (10 mg/m² IV)
 M - methotrexate (20 mg/m² IV)
 C - cisplatin (80 mg/m² IV)
 V - vinblastine (2 g/week IV)
 RT - radiotherapy

Fig. 1. Modified UICC-2 protocol chemotherapy for nasopharyngeal carcinoma.

neck dissection was performed together with nasopharyngeal biopsy.

All patients had radiation treatment on a cobalt-60 unit, five times weekly, with 1.8 or 2 Gy per fraction through two opposing lateral and one anterior fields. The irradiated volume was the nasopharynx, the base of the skull, the neck, and the supraclavicular region. The orbits and the larynx were shielded. A dose of 50–62.6 Gy was delivered to the primary site and of 30–50 Gy to the neck and supraclavicular region. In cases nos. 1 and 5, an electron boost up to a cumulative dose of 60 and 69 Gy, respectively, was added to the involved regional lymph nodes.

In one patient chemotherapy was given after he developed metastases (bleomycin, methotrexate, CCNU). In all other patients, chemotherapy was given as part of their primary treatment, together with radiotherapy. One patient received adjuvant chemotherapy according to the BACON protocol (bleomycin, doxorubicin, lomustine, vincristine) 4 weeks after completion of radiotherapy for a total of 4 cycles. In the other three patients, a combined chemoradiotherapy regimen was employed. It consisted of radiotherapy intercalated in a modified UICC-2 chemotherapy protocol for nasopharyngeal carcinoma (Figure 1). Sensitization with 2 g of vinblastine, once per week during irradiation, was performed in cases nos. 3 and 5. The doses of irradiation were adjusted to the response to prior chemotherapy.

The survival was calculated from the date of diagnosis until the date of death or last follow-up in December 1995. In all patients acute toxicity and late effects of therapy were evaluated.

RESULTS

Complete response of local and regional disease was observed in all patients. In patient no. 1, bone and liver metastases were diagnosed 6 months from completion of

primary therapy. Disseminated disease was treated with two cycles of chemotherapy and with irradiation of bony lesion but no objective response was observed and the boy died 15 months from diagnosis. The other four patients, all receiving a combination of radiation and chemotherapy as primary treatment, are alive with no evidence of disease 8 months and 6, 10, and 13 years, respectively, from diagnosis.

In all but one patient acute treatment toxicity was moderate. It included mucositis, loss of taste, xerostomia, dysphagia, and temporary weight loss. In patient no. 2, who received radiotherapy and adjuvant chemotherapy according to the BACON protocol, acute toxic manifestations were much more pronounced and temporary interruption of drug application as well as frequent blood transfusions were required due to severe pancytopenia. He also developed significant neck fibrosis, dentition problems and persistent xerostomia; substitutional therapy with thyroxine was introduced due to hypothyroidism. Patients nos. 3 and 4, both treated with combined chemoradiotherapy, experienced persistent xerostomia and in the latter, mild neck atrophy and dental caries were observed. Neuroendocrine evaluation of hypothalamic-pituitary axis did not reveal any abnormalities. Application of vinblastine during irradiation was not associated with increase of acute or late toxicity (Table 1).

DISCUSSION

Nasopharyngeal carcinoma in the young occurs most frequently in the early part of the second decade. It is characterized by its rarity, with an incidence of less than 1% of childhood malignancies [1], by its close association with Epstein-Barr virus infection [16], by the predominance of advanced loco-regional disease [2] and the somewhat better survival rates in the young than in adults, probably due to the histopathologic predominance of the undifferentiated type in younger patients [3,7]. When distant metastases occur, they do so within 24 months from diagnosis in most cases [4,5].

Radiotherapy is the accepted but not only treatment of UNC, with reported cures of 40–50% [10]. The optimal radiation dose for sustained control of UNC in the young is not defined. Ingersoll *et al.* recommended a dose of 62–66 Gy to the primary site, depending on T-stage, a dose of 50 Gy to the neck for subclinical disease and in case of palpable lymph nodes a dose of 56–66 Gy or even more to the neck was proposed, depending on the regional extent of disease [17].

Different chemotherapeutic schemes have been employed, given prior to, during or after radiation therapy [8–14]. Because the series of children with UNC are small and the patient age distribution as well as duration of follow-up varies, the results should be interpreted with

TABLE 1. Undifferentiated Nasopharyngeal Carcinoma in Children, 1972–1995: Clinical Characteristics, Treatment and Survival

Case No.	Age/Sex	Diagnosis		Radiotherapy			Chemotherapy protocol	Relapse			Follow-up	Current status	Late sequelae of treatment
		Date	Symptoms	TNM stage	Primary tumor	Lymph nodes		Date	Site	Therapy			
1	15 yrs./M	July 1979	Lymph node	T3N3M0 IV	60 Gy	60 Gy	—	April 1980	Bone Liver	RT Protocol no. 3	—	DOD 15 mos. NED	—
2	11 yrs./M	Sept. 1982	Lymph node Nasal obstruction	T4N3M0 IV	62.6 Gy	49.2 Gy	BACON	—	—	—	>13 yrs.	NED	Xerostomia Severe neck fibrosis Dental caries Hypothyroidism Xerostomia
3	16 yrs./M	March 1985	Lymph node Hearing impairment	T1N3M0 IV	50 Gy	50 Gy	UICC-2 vinblastine	—	—	—	>10 yrs.	NED	—
4	13 yrs./F	July 1989	Lymph node Earache Nasal obstruction	T3N2M0 IV	52 Gy	30 Gy	UICC-2	—	—	—	>6 yrs.	NED	Xerostomia Mild neck atrophy Dental caries
5	15 yrs./M	April 1995	Lymph node Epistaxis Hearing impairment Headache	T3N3M0 IV	54 Gy	69 Gy	UICC-2 vinblastine	—	—	—	>8 mos.	NED	—

DOD—dead of disease; NED—no evidence of disease.

caution. In any case, they suggest that combined modality approach might be effective in prolonging disease-free and overall survival compared with radiotherapy alone.

Our report of five UNC patients may support previous requests for effective systemic therapy [5,6]. In our series one patient who received only radiation therapy initially died. On patient, treated with combination of radiotherapy and adjuvant chemotherapy according to the BACON protocol is alive, with no evidence of disease 13 years after diagnosis, but went through severe early and late toxicity. Although effective, a combination of radiotherapy and adjuvant BACON protocol chemotherapy seems to be too aggressive. Pancytopenia, requiring treatment interruption and frequent blood transfusions, as well as late toxicity, make it less acceptable.

The other three patients were irradiated and chemotherapy was given according to a modified UICC-2 chemotherapy protocol for nasopharyngeal carcinoma. They are alive and free of disease 8 months and 6 and 10 years, respectively, from diagnosis. The acute toxic manifestations in these patients were only mild. Also, the late effects of treatment were much less pronounced in the latter group, with no neuroendocrine disturbances observed.

Our experience indicates that it may be advantageous to start treatment with chemotherapy, for better evaluation of its effect and safe reduction of the radiation doses in patients with a very favourable response to chemotherapy.

We are aware that the presented series is too small to allow any definitive conclusions. Nevertheless, we think some comments are warranted:

1. One patient, primary treated only with radiotherapy, developed hematogenous metastases, while those receiving also systemic chemotherapy are still in complete remission;

2. Combination of radiotherapy with 60 Gy tumor dose and adjuvant BACON protocol chemotherapy, although effective, was associated with severe early and late toxicity;

3. Lower dose radiotherapy combined with modified UICC-2 protocol for nasopharyngeal carcinoma seems to be equally effective but causing less morbidity.

Experience with the effect of combination of chemotherapy and lower doses of radiation in children with advanced UNC is very scanty. Lobo-Sanahuja *et al.* reported on five children treated with radiotherapy to a dose of 45 Gy and chemotherapy pre- and postradiation. The four survivors have too short follow-up to allow definitive conclusions [8]. Eight of the nine children reported by Roper *et al.*, were treated with irradiation to a dose of 30–49.5 Gy and adjuvant chemotherapy. Seven of the nine patients were reported to be alive and free of disease 19–86 months after diagnosis [9]. Our experi-

ence, limited as it is, nevertheless, with its long follow-up corroborates their results.

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